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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,874	04/25/2000	Jay Leng	CHEM1100	1721

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EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
09/559,874			

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Commissioner of Patents and Trademarks

Advisory Action	Application No. 09/559,874	Applicant(s) LENG, JAY	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08 May 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *08 May 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *See the attached Note of Explanation*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-47 and 63-68*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *See the attached Note of Explanation.*

NOTE OF EXPLANATION

1. The notice of appeal filed May 8, 2002 in Paper No. 10 is acknowledged and has been entered.

2. The amendment file May 8, 2002 in Paper No. 11 is acknowledged and has been entered. Claims 18 and 63 have been amended.

3. In the previous Office Action mailed October 31, 2001 (Paper No. 9), claims 18-30 were rejected under 35 USC § 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. More specifically, claims 18-30 were stated to be vague and indefinite because claim 18 recited the term "a corresponding change". In reply to the previous Office Action, Applicant has amended claim 18 as had been suggested to obviate the basis of this rejection. Therefore, the rejection of claims 18-30 under 35 USC § 112, second paragraph for the reason stated in section 14 of the previous Office Action is withdrawn.

4. Although the amendment filed May 8, 2002 has been entered, entry of the amendment fails to place this application in condition for allowance. Applicant's arguments have been carefully considered, but not found persuasive to overcome the grounds of rejection that had been maintained in the previous Office Action.

With regard to the grounds of rejection of the claims under 35 USC § 112, first paragraph, Applicant has for the most part, reiterated the arguments that were set forth in Paper No. 8 filed in response to the Office Action mailed March 9, 2001 (Paper No. 7). Applicant has suggested that a method comprising " 'contacting whole, live cells in isolation of the subject's body with an agent' is an *ex vivo* method", as opposed to an *in vivo* method. Applicant has further suggested that an *ex vivo* method is a type of *in vitro* method that is therefore encompassed by the claims. Also, Applicant has maintained that since coelenterazine is only added to the cells expressing luciferase just before the

15-second period during which the bioluminescence of the cells is measured, despite the cytotoxicity of coelenterazine, coelenterazine will have a nominal effect upon the cells, because the cells are only in contact with coelenterazine during this short period of time and the "cells will clearly not grow appreciably in only fifteen seconds" (page 7, paragraph 2). Applicant has also remarked that the specification teaches a sample of cell culture medium can be used as a control. Therefore, Applicant has contended that the issues raised as the grounds of the rejection of the claims under 35 USC § 112, first paragraph are immaterial. Additionally, contrary to the teachings of Cree, which suggest that the art is highly unpredictable, Applicant has contended that given the benefit of Applicant's disclosure, the claimed invention could be practiced successfully without need to engage in undue experimentation, since "the present invention is directed to *in vitro* methods, not *in vivo*" (page 8, paragraph 2). Furthermore, Applicant has remarked that the relationship between cellular proliferation and susceptibility to treatment with a cytotoxic agent is well known in the art.

In reply to Applicant's arguments, despite Applicant's suggested definition of the term "*in vivo*", Jasmin, et al have used the term to describe the bioluminescence of intact cells. In fact, Applicant's definition of "*in vivo*" is not fully commensurate with the scope of its meaning in the art. For example, generally a prokaryotic cell is not naturally part of a body of cells, and if the method is to be practiced using intact prokaryotic cells, the method might properly be termed an "*in vivo*" method, as has been evidenced, for example, by the teachings of Jasmin, et al. In further support of a less narrow definition of the term than that suggested by Applicant, the Biology-Online Dictionary of Biology defines "*in vitro*" as "[b]iological processes or reactions that would normally occur within an organism but are made to occur in an artificial environment, i.e. a laboratory", and defines "*in vivo*" as "[o]ccurring within a biological organism". Accordingly, it is evident that bioluminescence produced by an intact cell is properly referred to as an "*in vivo*" process, and a method for measuring the bioluminescence produced by an intact cell may be properly referred to as an "*in vivo*" method. As stated in the previous Office Action, although the claims recite the limitation "*in vitro*", the claims encompass a method in which whole, live cells in isolation of a subject's body are exposed to

coelenterazine, which is a substrate for luciferase. After a cell takes up coelenterazine, bioluminescence is produced upon the reaction of coelenterazine and luciferase. As stated in the previous Office Actions, Jasmin, et al teach, "[i]n all instances, a key requirement for the application of bioluminescence is the establishment of a strict correlation between *in vivo* bioluminescence and cell viability, as determined by colony counting on agar plates" (abstract). Of course, since eukaryotic cells are not cultured on agar plates, as are prokaryotic cells, it would be necessary to establish a strict correlation between *in vivo* bioluminescence and cell viability by another method amenable to the analysis of the proliferation of eukaryotic cells. Nevertheless, as stated in the previous Office Actions, the guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims, since, in particular, the specification fails to exemplify the claimed method for measuring the proliferation of intact cells in the presence or absence of a therapeutic agent or to establish a strict correlation between *in vivo* bioluminescence and cell viability as Jasmin, et al teach would have been necessary to enable the skilled artisan to practice the claimed method with a reasonable expectation of success without the need to perform additional, undue experimentation.

Furthermore, although Applicant has asserted that the method can be practiced by exposing intact cells to coelenterazine for a mere 15 seconds, a time period of such brevity that the cytotoxicity of the coelenterazine would not likely affect the results of the analysis, Applicant has failed to provide any factual evidence to support this assertion. As the method is not exemplified in the specification, there is no evidence of record that the method can be used successfully. It is reasonable to question that sufficient coelenterazine will have been taken up by the cells and will have reacted with luciferase within the cell to produce sufficient bioluminescence during the 15 second period to which Applicant has referred. It is reasonable to question that the assay will be sensitive enough to reliably and accurately determine differences in the viability of the cells in the presence and absence of a cytotoxic agent. However, if longer periods of exposure to coelenterazine prove to be required in practicing the claimed method, then the problems and limitations set forth in the previous Office Action must be addressed.

Finally, the fact that the relationship between cellular proliferation and susceptibility to treatment with a cytotoxic agent is well known in the art, it not germane to the enablement inquiry in this instance, since the relationship to which Applicant refers has been established using methodology other than the methodology claimed in this application, but it is the former methodology that Jasmin, et al have suggested would be needed to establish a strict correlation between *in vivo* bioluminescence and cell viability. Because Applicant has not established this strict relationship between *in vivo* bioluminescence and cell viability, contrary to Applicant's assertions, given only the benefit of Applicant's disclosure, the skilled artisan could not practice the claimed method with a reasonable expectation of success without the need to first perform additional, undue experimentation.

With regard to the grounds of the rejection of the claims under 35 USC § 112, second paragraph, again, Applicant has for the most part, reiterated the arguments that were set forth in Paper No. 8 filed in response to the Office Action mailed March 9, 2001 (Paper No. 7). As it appears that Applicant has not set forth any new grounds of traversal, Applicant is referred to the response to Applicant's remarks in Paper No. 9, since Applicant's arguments have been addressed therein.

With regard to the grounds of rejection of the claims under 35 USC § 103(a), once again, it appears that Applicant has not set forth any new grounds of traversal. Therefore, again, Applicant is referred to the response to Applicant's remarks in Paper No. 9, since Applicant's arguments have been addressed therein.

Accordingly, Applicants' arguments have been carefully considered but have not been found persuasive. Therefore, the grounds of the rejections of the claims under 35 USC §§ 112 and 103, which were set forth in the Office Action mailed March 9, 2001 (Paper No. 7) and maintained in the previous Office Action mailed October 31, 2001 (Paper No. 9), are again maintained.

Conclusion

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 31, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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